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Short report

Oncopolicy in high-income countries can make a difference in HPV-related Head and Neck Cancer☆☆

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ABSTRACT

The Human Papilloma Virus (HPV) is a causal agent in a subset of Head and Neck Cancers (HNC), which is being diagnosed in younger men without a significant history of tobacco and alcohol use. The increasing incidence of these cancers and the burgeoning cost associated with treatment should make this issue a legitimate oncopolicy agenda priority. This communication details a number of actionable strategies that policy-makers could implement to reduce the number of people diagnosed with the disease, enhance the quality of life for those living with the disease and lessen the likelihood of dying from the disease.

Based on a HPV and Head and Neck Cancer symposium held in National University of Ireland, Galway on May 17th 2013. We make the argument that a supra-regional, multidisciplinary, research-focused approach to HPV-related HNC is urgently needed. Policy-makers could support a network of researchers in the fields of epidemiology, pathology, clinical treatment, health economics and public health to work together to raise public awareness about the disease, treat patients to the highest international standards and evaluate prevention strategies such as gender-neutral HPV vaccination. We hope that this communication will hold sway in many high and middle-income countries.

Background and context

The seminal paper linking HPV and a subset of Head and Neck Cancers (HNC) was published relatively recently in 2000 [1]. The lymphoepithelium of the oropharynx (i.e. Base of tongue, Waldyer's ring, tonsillar fossa and lingual tonsils) is the primary site for HPV-related HNC. These cancers have been accepted as a distinct epidemiologic, clinical, and molecular entity [2]. Comparison of the known epidemiology of HPV-related and unrelated HNC is given in Table 1.

In the US, the latest estimated annual incident cases of HPV-associated HNC (~12,989) have now surpassed cervical cancer (~11,388) and look set to increase [4]. In France, the estimated annual costs of treating HPV-associated HNC in men (€94.6million) is greater than invasive cervical cancer (€83.9million) in women [5]. Many unanswered questions remain about the natural history of these cancers, how best to treat HPV-positive HNC and the effectiveness of HPV prophylactic vaccines against oral HPV infection [6]. The actionable content that follows outlines practical policy recommendations in different disciplines to counter the rise of these cancers.

Epidemiology

The Korean cancer registry is the latest group to report trends in population-level HPV-related HNC sites based on International Classification of Disease (ICD) codes [7]. A more costly and scientific approach, adopted in Ireland, involves retrospective analysing archival tissue samples for HPV. Either epidemiologic approach provides 'baseline' information to policy-makers regarding the likely burden of this disease in their jurisdiction.

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Table 1
Comparison of the general epidemiology of HPV related and unrelated Head and Neck Cancers (HNC) [3].

	HPV-related HNC	HPV-unrelated HNC
Incidence trend	Increasing	Decreasing/stable
Anatomic location	Primarily tonsil and base of tongue	All head and neck sites
Median age (year) at diagnosis	54	60
Socioeconomic status	Higher	Lower
Primary risk factors	Sexual exposure to oral HPV	Tobacco and alcohol exposure
Survival	Better	Worse
3-Year oropharyngeal survival (%)	82	57

The prevalence of oral HPV at population level was recently estimated in the US by utilizing an established national representative survey – National Health and Nutrition Examination Survey (NHANES) [8]. Survey participants gargled a 30-second oral rinse that underwent HPV DNA analysis. The results showed that 6.9% of adults and teenagers (14–69 years) were infected with oral HPV of any kind. Only 1% of the population was infected with HPV-16, the strain most linked to oropharyngeal and cervical cancer. Oral HPV infection was three times more prevalent in men than in women, dovetailing with the rate of HPV-related oropharyngeal cancers now seen in the US. Stratifying the data by age shows a bimodal distribution with peaks in individuals aged 30 to 34 years (7.3%; 95% CI, 4.6–11.4%) and 60 to 64 years (11.4%; 95% CI, 8.5–15.1%).

Without the appropriate population-level research vehicle to collect oral rinses and test for HPV, researchers, like those in Scotland, are embarking on prevalence feasibility study using dental practices. We recommend that any oral HPV prevalence study be repeated periodically to help establish the natural history of the infection and estimate the impact HPV vaccination has on the prevalence of oral HPV.

Pathology

In 2011, the College of American Pathologists and the American Joint Committee on Cancer added routine HPV testing as part of the standard pathologic evaluation of resected oropharyngeal squamous cell carcinomas (OPSCC) for the purpose of molecular tumour staging. HPV testing of clinical samples is useful for establishing the site of tumour origin for patients presenting with metastatic disease, for guiding therapy, for educating/counselling patients, and for estimating clinical outcomes [9]. Indeed, HPV-positive OPSCC is associated with significantly lower all-cause and cancer specific mortality adjusting for covariates and detection methods [10]. Therefore, HPV status is now recognized as the most important independent prognostic variable.

There is currently no standard approach for HPV testing of clinical samples. Instead, methods of HPV testing across laboratories vary considerably reflecting the biases and tendencies of individual investigators. Detection strategies vary not just in design, but in their detection targets. These targets have included HPV DNA, HPV RNA, viral oncoproteins, cellular proteins and HPV-specific serum antibodies. For widespread implementation in the clinical arena, detection methods must be accurate, technically feasible and cost-effective. Most laboratories use 1 of the 2 HPV DNA detection methods – Polymerase Chain Reaction (PCR)-based amplification or In Situ Hybridization (ISH). Immunostaining for p16 protein has recently been regarded as a practical alternative or complementary procedure for HPV testing of oropharyngeal cancers based on a high correlation between the HPV detection and p16 overexpression in recent studies. Indeed, the simplicity, low cost and high sensitivity of p16 immunohistochemistry have prompted consideration of replacing more intensive ISH and PCR-based methods as a standalone HPV test.

The successful development of detection assays optimized for cytological samples [e.g. fine-needle aspirations (FNA) of neck metastases using liquid phase assays (e.g. Hybrid Capture 2 assay)] will open the door to more widespread implementation of HPV testing, and may obviate expensive tissue acquisition and processing [11]. A multi-centred trial of the clinical and cost-effectiveness of FNA in an outpatient/clinic care setting seem warranted. Moreover, it is imperative that HPV testing of OPSCC be routinely conducted. Policy-makers should encourage that standardized HPV pathology guidelines be implemented in hospitals treating OPSCC patients.

Work-up, clinical trials and treatment

The work-up of a suspected HPV-related HNC patient should include detailed patient history (i.e. presenting symptoms, risk profile), physical examination (i.e. primary site inspection and palpation, neck nodules, radiography) and biopsy (i.e. examination under anaesthesia and HPV testing) [12]. Development of a work-up checklist system would ensure that universal standards of care would occur across various regional treatment centres. It would be prospectively appropriate for cancer registries to record HPV/p16 status along with other health behaviours such as smoking and alcohol use for all HNC patients.

Currently, HPV-positive and negative OPSCC are treated similarly even though they are very different diseases. Treatment options are usually multimodality that includes laser/robotic surgery, radiation and various chemotherapy agents. To categorically avoid biases, growing consensus among cancer investigators exists to support the opening of phase II/III trials that strictly study either HPV-positive disease or HPV-negative disease [13]. The favourable responsiveness of HPV-positive OPSCC to current treatment represents an exciting opportunity for studying careful treatment deintensification to reduce acute toxicity and improve long-term patient recovery. We recommend that cost and functional outcomes/quality of life research form part of the trial design to inform evidence-based policy making.

While awaiting the results of large US studies (e.g. E1308 & RTOG 1016) and UK studies (e.g. De-ESCLaTE HPV, REALISTIC), a model of shared decision-making could be promoted by policy-makers. This model of care, advocated by Johns Hopkins Hospital, encourages patients to meet with head and neck surgeons, medical oncologists, radiation oncologists, and speech language pathologists in one clinic visit. After review of medical records, pathology, imaging studies and physical examination, a consensus opinion regarding management is given. This process of shared decision-making gives the patient and his/her caregivers the opportunity to openly discuss pros and cons of various treatment and management options with all disciplines present.

Public awareness of HPV-associated HNC

In June 2013, Hollywood actor, Michael Douglas, in a candid interview with the Guardian newspaper in England, made reference to HPV as a causal agent in HNC. The interview created a large media attention on the risk factors (i.e. oral sex) involved in HPV-associated HNC. A legacy of the 'Michael Douglas' media story is to address the social stigma associated with HPV. As an infection spread by intimate contact, HPV is ubiquitous among the sexually active. The reason why only a very small proportion of infected individuals go on to develop HPV-related HNC are currently unknown, but complex interactions between the virus and the host immune system appear to play very important roles. In the emerging social media era, we recommend that each jurisdiction develop a public health campaign that uses video and infographics to convene their

message in the social media era [14]. Mount Sinai Medical Center, New York produced an excellent infographic entitled: "Can I get cancer from oral sex?"

Patient-led interest groups like the Throat Cancer Foundation in Scotland and HPVandme.org in San Francisco have emerged recently to raise awareness of HPV and HNC. Many more survivors of this cancer are bravely sharing their stories in various media outlets and actively campaigning for more research into treating and preventing this form of cancer.

Early detection and prevention strategies

Cervical cancer screening is effective in detecting precancerous lesions caused by HPV. Given the inaccessibility of the oropharynx and lack of known precancerous lesions, a similar screening technique is more difficult to perform for suspected HPV-related HNC. Encouragingly, early detection may be possible by a blood test. Using the European Prospective Investigation into Cancer and Nutrition cohort, investigators showed that HPV16 E6 seropositivity was present more than 10 years before diagnosis of oropharyngeal cancers [15].

Public health practitioners are genuinely optimistic that HPV vaccination will prevent future HPV-associated cancers. In 2013, policy-makers in Australia added boys to their school-wide HPV vaccination programme. However, an opposing polemic development occurred in Japan, as the Health Ministry withdrew support for the vaccine to implement investigations into its safety. Currently in Europe, HPV vaccinations are not licensed for cancer prevention in males. Pharmaceutical manufacturers are likely to seek reimbursement for cancer prevention in males and for future health technology assessment of gender-neutral HPV vaccination; detailed HPV-associated HNC cost-of-care studies are needed to assess the cost-effectiveness of vaccinating both sexes. As politics play a critical role in health policy formation, HPV vaccination in girls has already been a contentious issue in many countries. We'd encourage 'open' debate with a consultation process. However, a strong emphasis on scientific evidence ought to inform decision-making and this communication sets out a number of key studies to gather such vital information.

Conclusion

We strongly feel that within each patient is an opportunity to learn more about this emerging disease. Clinicians should not only treat the patient but also advance the field by enrolling patients into clinical trials or functional outcome studies. Moreover, we believe that supportive oncopolicy of multidisciplinary collaboration (See Table 2) can make a huge difference in tackling this potentially modifiable disease.

Table 2
Proposed multi-disciplinary policy initiatives.

Discipline	Achievable policy initiatives
Epidemiology	• Retrospective analysis of sample tissue for HPV in associated HNC sites • Oral HPV prevalence studies
Pathology	• Routine testing of oropharyngeal cancer for HPV & p16 biomarker • Standardisation of HPV detection methods • Prospective HPV/p16 status recording by registries • Funding to determine the cost-effectiveness of using Fine Needle Aspiration (FNA) for early detection
Clinical management	• Standard work-up checklist for HNC Physicians • Enrol patients in clinical trials and functional outcome studies • Shared decision-making with patient involvement
Health economics	• Cost-of-care study of HPV-related HNC • Gender neutral HPV vaccination evaluation
Public health	• Investment in an awareness campaign • Primary care education of signs and symptoms • 'Open' consultation process with medical organisations, advocacy groups, faith organisations, pharmaceutical industry and other stakeholders to implement policy

Conflict of interest statement

No conflict of interest.

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